THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 31y female with amenorrhea"

Dr. Umans does not have any relevant financial relationships with any commercial interests.

Learning Objectives

- 1) Review potential causes of secondary amenorrhea in diabetes patients
- 2) Discuss the effect of diabetes on the hypothalamic-pituitary-ovarian axis

Case Presentation

- 31yF with known Type 1 Diabetes presented to the UCMC ED with acute worsening of vision
- She was previously admitted several months prior, with a CAUTI and C. difficile infection. She was advised to follow up with ophthalmology following her discharge for her subacute worsening of her vision. She was later seen by an outside ophthalmologist who advised admission for urgent procedures to salvage her minimal remaining vision.
- She was evaluated in the emergency department by ophthalmology and was admitted with concerns for tractional retinal detachment

Past medical history

- **Diagnosis:** age 19, patient reports that she was initially diagnosed as GDM but later told she had Type 1
- **Blood sugars:** Checking 3 times per day with mother's assistance
- **Med compliance:** reports that she has historically not always cared for her diabetes regularly, but has gotten "more on top of it" in the past 2 months
- Diabetes complications: retinopathy, autonomic neuropathy (neurogenic bladder with chronic indwelling foley, and orthostatic hypotension)

At a recent stay at another hospital, an outside physician had reported concerns for possible adrenal insufficiency, and empirically started hydrocortisone and fludrocortisone

ROS

- General: no fevers, weight changes
- HEENT: +acute worsening of vision loss
- Cardio: no chest pain, palpitation, dyspnea or LE swelling. +Orthostatic hypotension
- Pulm: no cough, dyspnea, or sputum production
- GI: persistent diarrhea, no abdominal pain, no nausea or vomiting
- GU: +amenorrhea since the age of 24, +neurogenic bladder
- MSK: no fractures or deformities
- Integumentary: new bullous lesions on hands

- Menarche- age 12, reports regular menstrual cycles during adolescence and post-partum. Menstrual cycles abruptly stopped at age 24. She reports that she has never been evaluated for this concern

Physical exam

- General: not acutely distressed
- HEENT: pupils dilated with crusting of eyelashes
- Neck: no thyromegaly or palpable nodules
- Card: regular rate and rhythm
- Pulm: unlabored breathing, clear to auscultation
- Abd: soft, nontender, nondistended
- GU: +foley
- MSK: no deformities
- Skin: no acanthosis, no lipohypertrophy at insulin injection site, no hirsutism, +bullae on fingers/dorsum or hands

-What etiologies are you considering for her amenorrhea?
-What work up would you order?

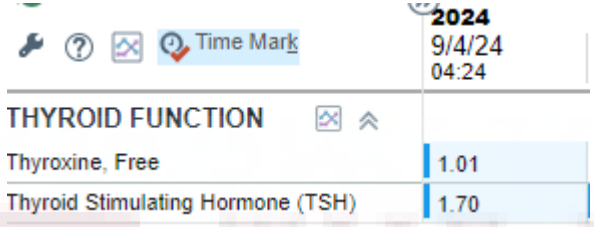
Initial Labs

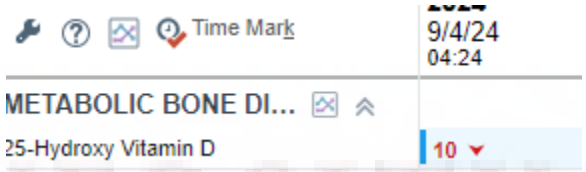
Time Mark	2024 9/8/24 13:33	9/5/24 05:28	9/4/24 04:24
ENDOCRINOLOGY			
ACTH		19.9	
BHCG, Plasma, Quant.		<2.0	
Cortisol		9.1	
Estradiol, Serum		<20	
FSH			3.6
LH			0.5
Prolactin			3.58 ↓
DHEA-S		64.9 ↓	
Pregnancy Test, Ur	Negative		

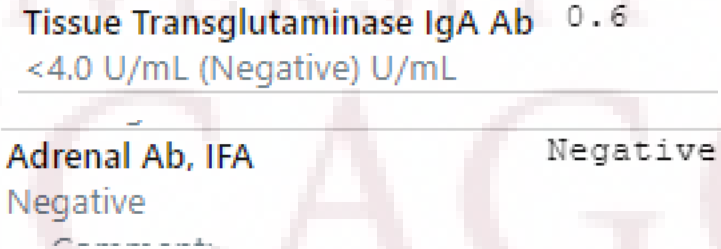
Total Testosterone 20 - 60 ng/dL	13 ↓
Sex Hormone Binding Globulin 20 - 100 nmol/L	36
Albumin 3.5 - 5.0 g/dL	4.0
Free Testosterone (Calculated) 3 - 9 pg/mL	4

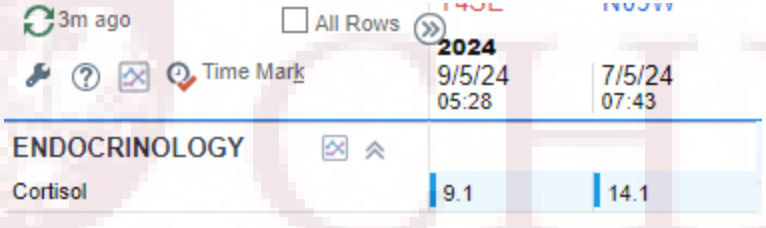
BASIC & COMPREHE...	
Glucose, Ser/Plasma	112 ↑
Glucose	
Sodium	141
Na+	
Potassium	3.9
K+	
Chloride	111 ↑
Cl-	
Carbon Dioxide	20 ↓
Anion Gap	10
BUN	22 ↑
Creatinine	1.22
eGFR, All	61 ↓
Calcium	9.4
Inorganic Phosphate	3.8
Magnesium	1.9
Total Protein	7.9
Albumin	3.9
Bilirubin, Total	0.3
Bilirubin, Conjugated	<0.1
Bilirubin, Unconjugated	See detail
Alk Phos, Serum	84
AST (SGOT)	9
ALT (SGPT)	19

Additional labs





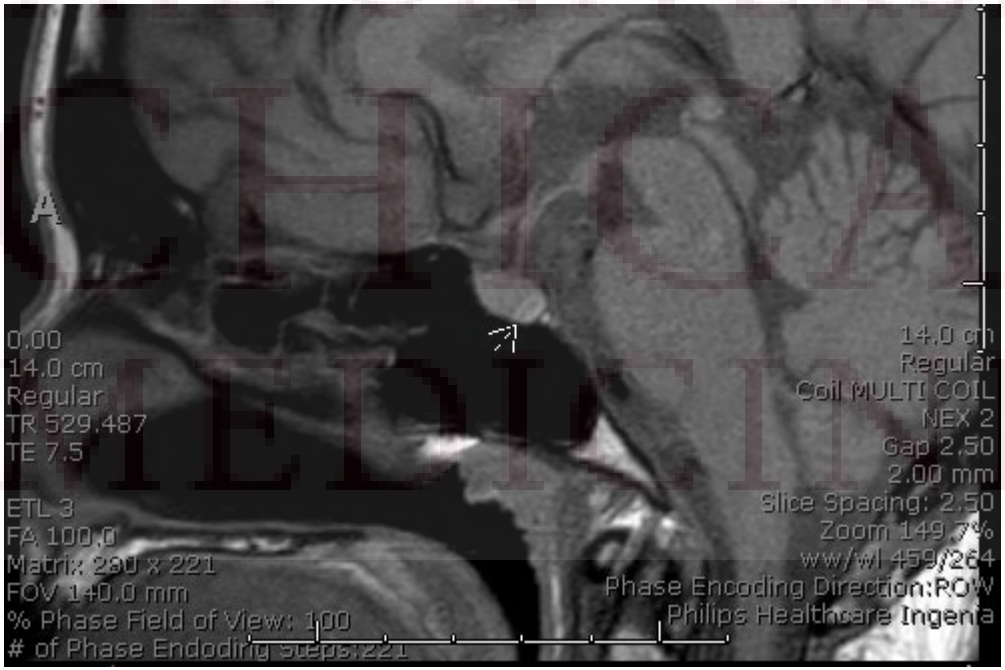




Pituitary Imaging

IMPRESSION:

A focus of mild T1/T2 hyperintensity in the midline along the posterior aspect of the pituitary may reflect a prominent posterior pituitary bright spot or Rathke cleft cyst. No pituitary adenoma is identified.



Type 1 Diabetes and the HPG axis

Amenorrhea Causes

- Hyperandrogenism
- Anatomic abnormalities
- DSD (gonadal dysgenesis, 5 alpha reductase deficiency)
- Hypergonadotropic
  - Autoimmune polyglandular syndrome
  - POI
- Hypogonadotropic
  - Hypothalamic amenorrhea
  - Pituitary adenoma

TABLE 5. Prevalence of earlier episodes of amenorrhea among diabetic women aged 18–49 yr; relation to time for debut of diabetes mellitus

	Primary amenorrhea[a]		Secondary amenorrhea[b]	
	Absolute	Relative %	Absolute	Relative %
All diabetic women	12	4.9[c]	26	10.7[c]
Women with debut of diabetes before or at the time at menarche	11	4.5[c]	24	10.0[c]
Women with debut of diabetes after the time at menarche	1	0.4	2	0.8
Controls	3	1.2	12	4.8

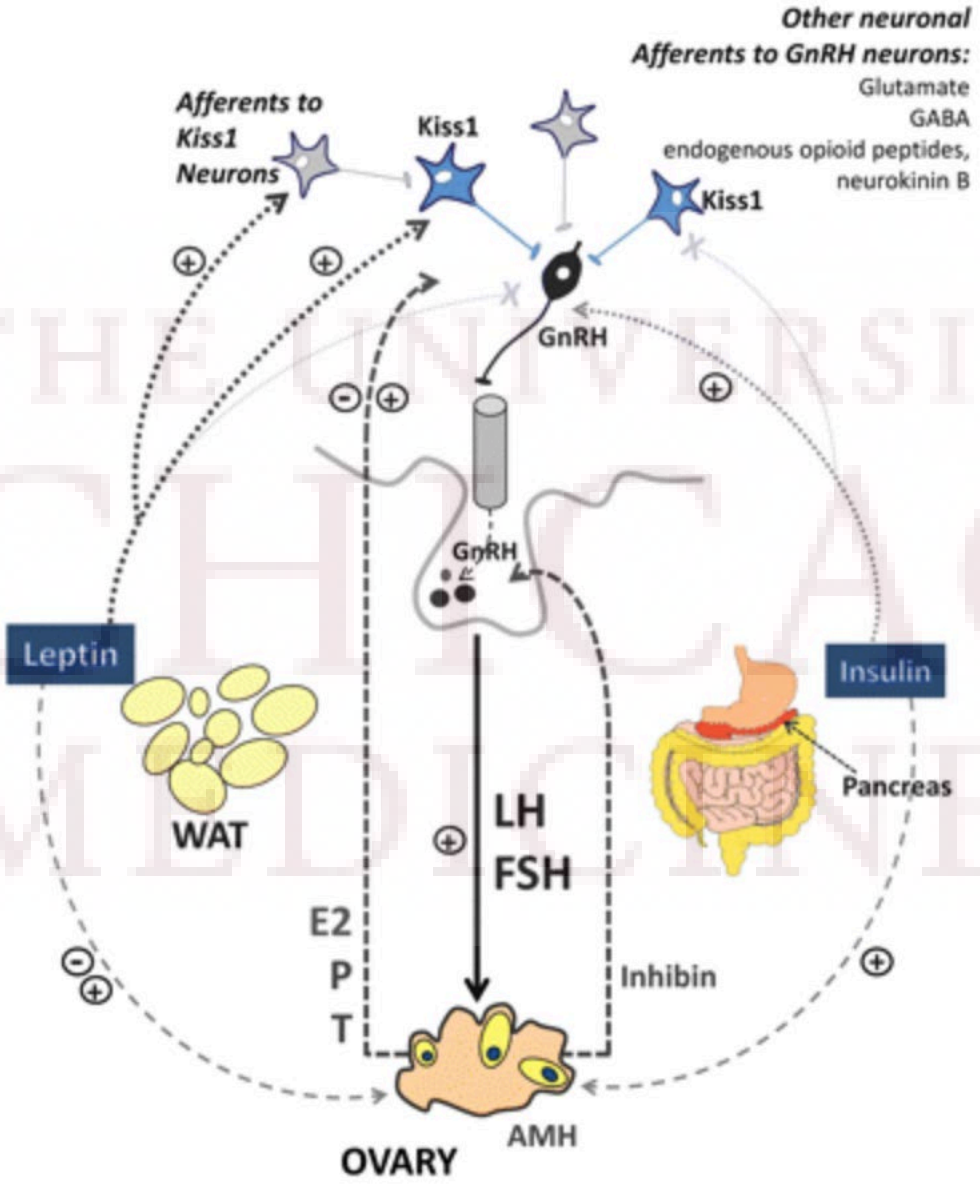
[a] Number of respondents, 245 for the diabetic group and 249 for the control group.

[b] Number of respondents, 243 for the diabetic group and 250 for the control group.

[c] Significantly different from controls ($P < 0.05$).

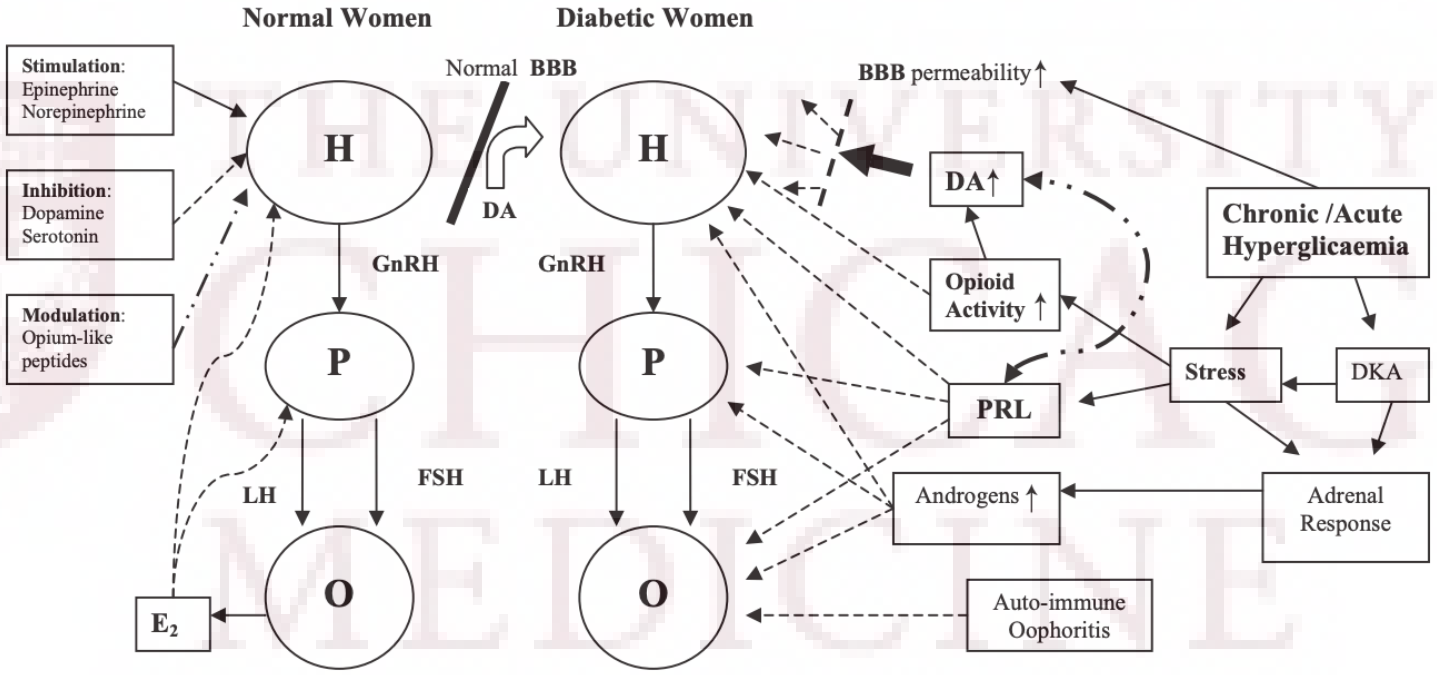
Table 3. Characteristics of menstrual cycles according to metabolic control in girls with type 1 diabetes mellitus compared with the control group.

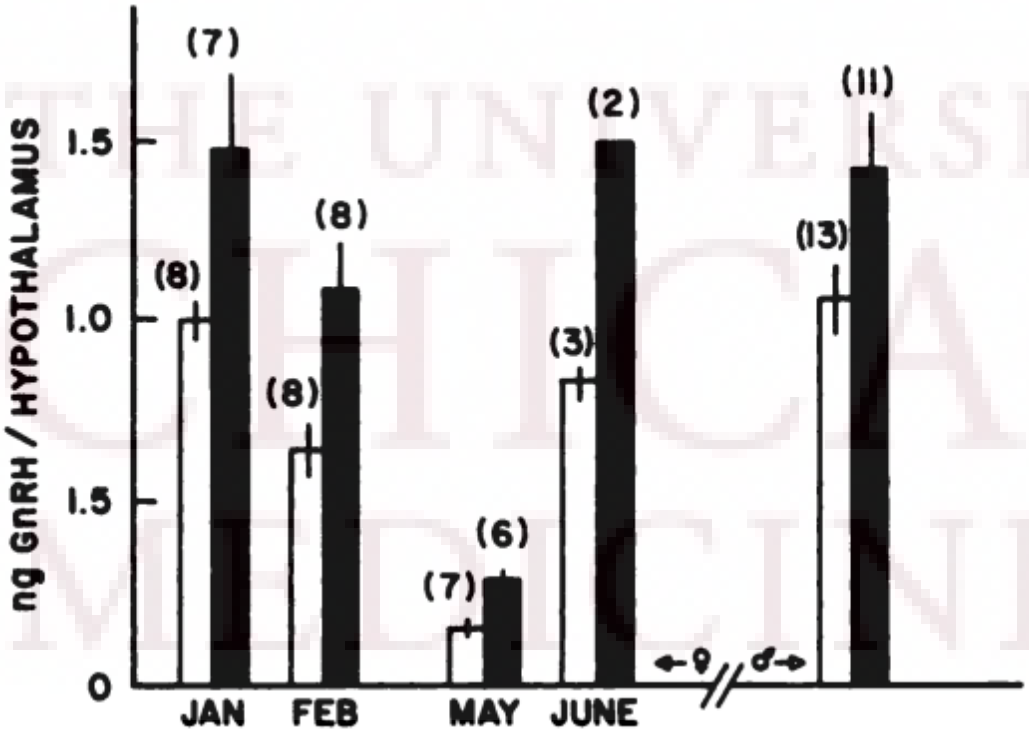
	Type 1 diabetes mellitus; HbA1c (%)			
	<7.6	**7.6–8.9**	**>9**	**Control**
No.	15	18	23	56
Menarche (y)	12.2 ± 0.9	12.5 ± 1.4	13.0 ± 1.3[a]	12.1 ± 1.0
Menstrual cycle duration (d)	34.9 ± 8.9	48.6 ± 34[b]	57 ± 52.3[c]	32.0 ± 6.9
CV (%)	27.6 ± 15.6	35.5 ± 17.8[b]	27.4 ± 21.7	23.7 ± 18.4
Girl had at least one cycle with				
Oligomenorrhea (%)	53.3[b]	72.2[c]	54.5[a]	19.6
Amenorrhea (%)	0	11.1	18.2[b]	1.8
Polymenorrhea (%)	60.0	50.0	18.2[b]	44.6

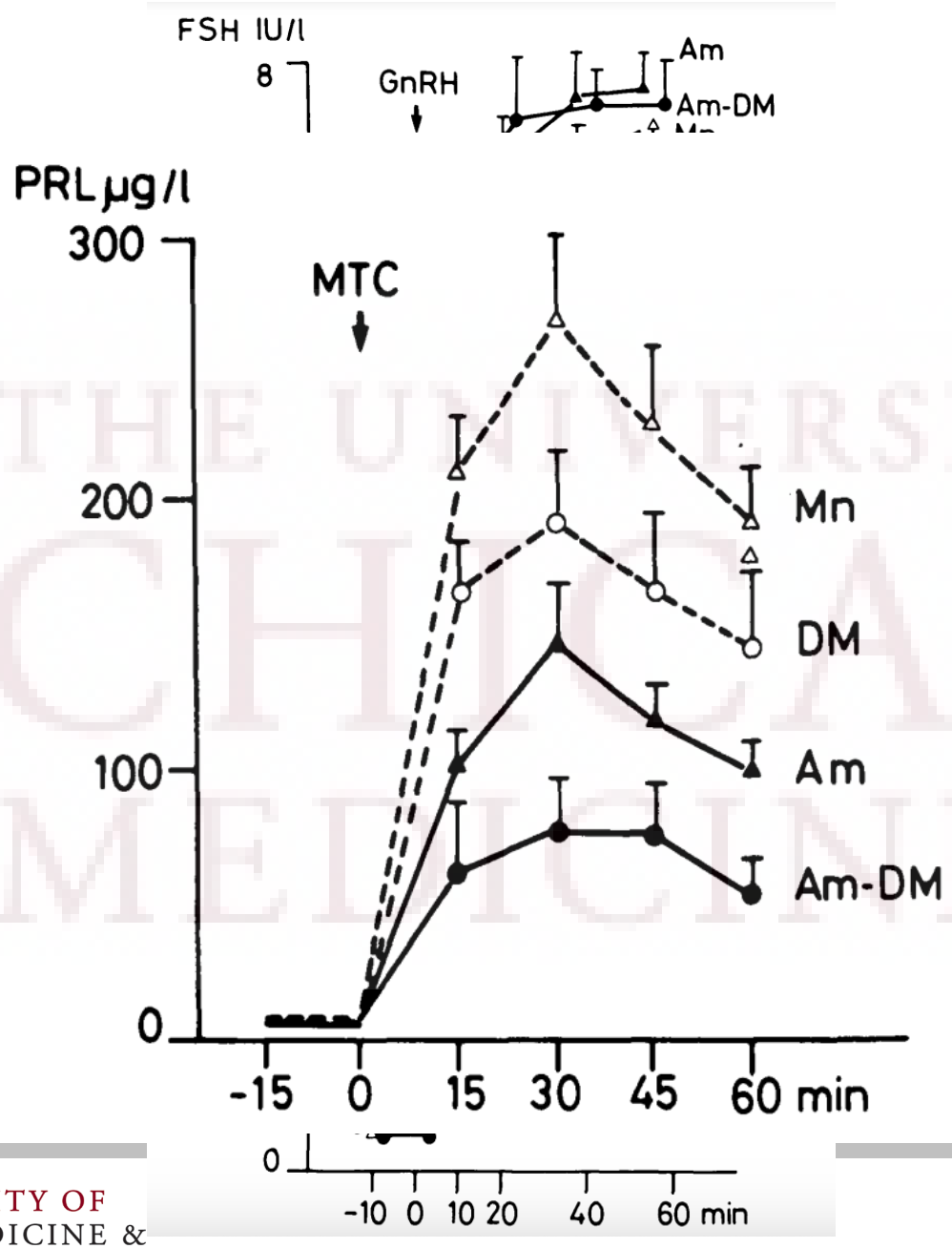

Other neuronal
Afferents to GnRH neurons:
Glutamate
GABA
endogenous opioid peptides,
neurokinin B
Afferents to
Kiss1
Neurons
Kiss1
Kiss1
GnRH
GnRH
Leptin
Insulin
WAT
Pancreas
LH
FSH
E2
P
T
Inhibin
AMH
OVARY

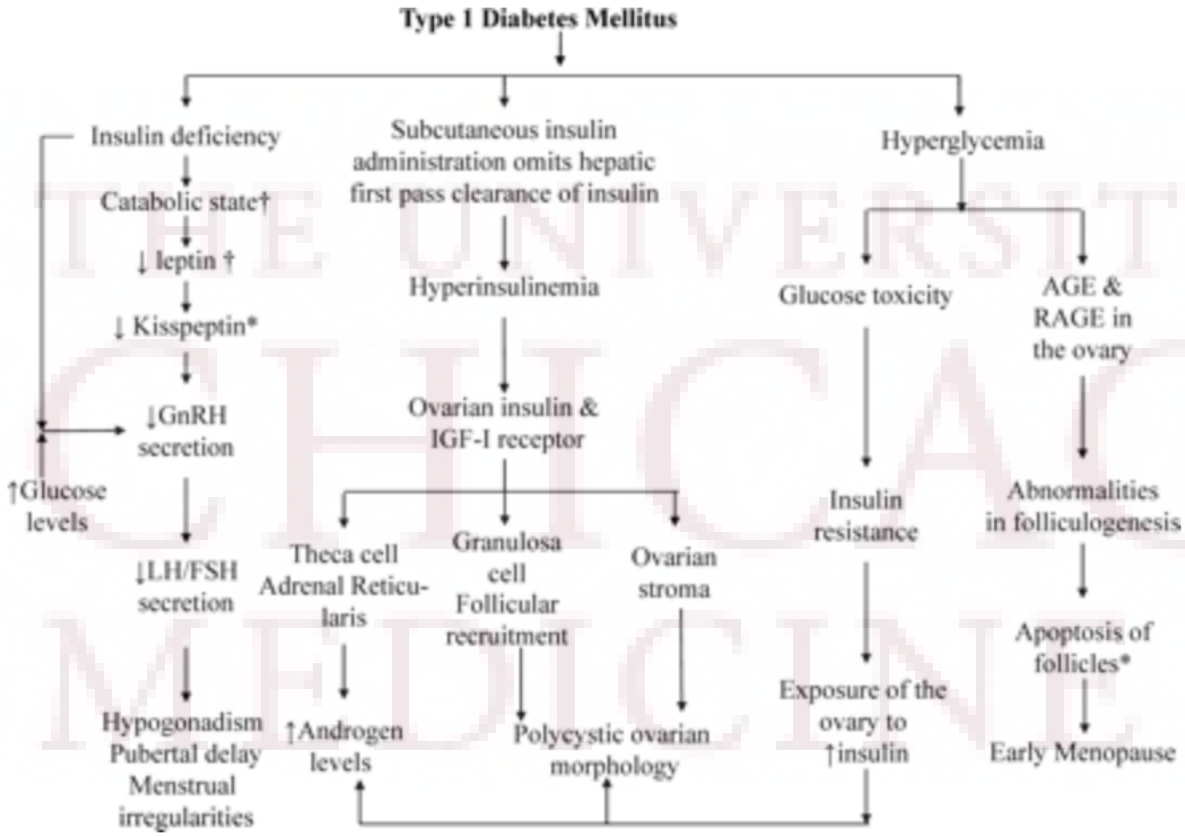
Potential Mechanisms of HPO dysfunction

- Catabolic state→ decreased leptin
- Increased dopaminergic response to hyperglycemia and ketosis
- Increased endogenous opioids
- Low levels of FSH/LH with decreased responsiveness to GnRH


Normal Women
Diabetic Women
Stimulation: Epinephrine Norepinephrine
Inhibition: Dopamine Serotonin
Modulation: Opium-like peptides
Normal BBB
DA
H
H
GnRH
GnRH
P
P
LH
FSH
LH
FSH
O
O
E2
BBB permeability
DA
Opioid Activity
Chronic /Acute Hyperglicaemia
Stress
DKA
PRL
Androgens
Adrenal Response
Auto-immune Oophoritis


ng GnRH / HYPOTHALAMUS
1.5
1.0
1.5
0
(7)
(8)
(8)
(8)
(7)
(6)
(3)
(2)
(13)
(11)
♀
♂
JAN
FEB
MAY
JUNE


FSH IU/l
8
GnRH
Am
Am-DM
PRL µg/l
300
200
100
0
MTC
Mn
DM
Am
Am-DM
-15
0
15
30
45
60 min
0
-10
0
10
20
40
60 min


Type 1 Diabetes Mellitus
Insulin deficiency
Catabolic state↑
↓ leptin ↑
↓ Kisspeptin*
↓GnRH secretion
↑Glucose levels
↓LH/FSH secretion
Hypogonadism
Pubertal delay
Menstrual irregularities
Subcutaneous insulin administration omits hepatic first pass clearance of insulin
Hyperinsulinemia
Ovarian insulin & IGF-I receptor
Theca cell Adrenal Reticu-laris
Granulosa cell Follicular recruitment
Ovarian stroma
↑Androgen levels
Polycystic ovarian morphology
Hyperglycemia
Glucose toxicity
Insulin resistance
Exposure of the ovary to ↑insulin
AGE & RAGE in the ovary
Abnormalities in folliculogenesis
Apoptosis of follicles*
Early Menopause

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ENDORAMA

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